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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,211	11/14/2003	Joseph Edward Zahner	NR 03-001	5750

32809 7590 09/20/2007

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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	**PAPER NUMBER**
1632	
MAIL DATE	**DELIVERY MODE**
09/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,211	ZAHNER, JOSEPH EDWARD	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Matters

1. This application has been transferred to a new examiner. The new examiner is Marcia S. Noble.

Status of Claims

2. Claims 1-12 are pending and under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-12 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant traverses this rejection on the following grounds:

Applicant asserts that the rejection is based on the premise the specification bases its analysis of reprogramming solely on morphological analysis and that treated keratinocytes appear neuron-like in nature. Applicant points out that this is not the case, and the specification provides semiquantitative RT-PCR analysis (Figure 2) to

demonstrate that the keratinocytes express an increase in neurofilament mRNA of 89% above levels detected in keratinocytes before treatment, which demonstrates that the cells express a marker associated with ectodermal cell lineage. Applicant also suggests that the keratinocytes expressed alpha-1-antitripsin and cardiac actin after treatment suggesting that the cells were expressing non-keratinocyte genes that represent ectodermal, mesodermal, and endodermal linage derived cells (page 1-2 of remarks, filed 1/22/2007).

This argument has been fully considered and is not found persuasive. It is acknowledged that Applicant has provided more evidence than morphological data. However, the data provided by Applicant is insufficient to demonstrate that the treated keratinocytes are reprogrammed into non-keratinocyte cells. Applicant has provided that treated keratinocytes produce markers of various cell lineages in addition to morphological data. However, expression of other genes not normally expressed in keratinocytes after being treated with agents known to alter transcription of various gene does not demonstrate that the treated keratinocytes has become another cell type. These results do not demonstrate that the keratinocytes now have the capability to function as a neuronal cell, cardiac cell, or any other cell type. It has only demonstrated that the cell can express non-keratinocyte genes after treatment with agents that have been known to turn on and turn off other gene transcription activities and can not be distinguished from aberrant gene expression associated with the treatment with demethylation and deactylation agents. Therefore, it is not clear that the method as claimed will result in the reprogramming of keratinocytes.

Applicant asserts that Examiner's position that the specification does not provide support for the full breadth of the claims and that the claims encompass reprogramming keratinocytes into any cells types, totipotent, pluripotent, or any differentiated cell type is incorrect. Applicant asserts that the claims encompass reprogrammed cells that express a telomerase gene product, which is not expressed in keratinocytes. Applicant asserts that the specification teaches the treatment of keratinocytes with chromatin altering agents that result in increased expression of telomerase mRNA (p. 2 of remarks, filed 1/22/2007).

This argument has been fully considered but is not found persuasive. To clarify the previous Examiner's position, the breadth of the instant claims encompass reprogramming keratinocytes into any cell type, be it totipotent, pluripotent, such as ES cells, or any type of differentiated cell. The process of reprogramming is most commonly associated with inducing a differentiated cell to obtain a less differentiated state. However, the breadth of reprogramming can also encompass the process of trans-differentiation, which encompasses causing a differentiated cell of one type to become a differentiated cell of another type. Trans-differentiation and de-differentiation are not considered the same processes in the art, yet the claims encompass the same processes resulting in the same outcome. The specification suggests that treatment with chromatin altering agents results in pluripotent cells because the treated keratinocytes express mRNAs expressed by multiple different non-keratinocyte cells. This in particular would not support the process of trans-differentiation as is encompassed by the claims. Furthermore, as stated above, the expression of non-

keratinocyte gene by the keratinocytes treated with chromatin altering agents does not in itself demonstrate that the treated keratinocyte is and functions as another non-keratinocyte cell type, therefore not supported the method as a method of dedifferentiation as well. Similarly, while it is acknowledged that telomerase is associated with pluripotency, expression after chromatin altering agent treatment in itself does not demonstrate reprogramming for the same reasons discussed above.

The enablement rejection of record provided several arts that would suggest treatment with chromatin altering agents in themselves would not reprogram a differentiated cell. The enablement rejection of record cites Kikyo et al (2000) which suggests that the only method known in the art for returning a nucleus of a somatic cell to a more pluripotent state is the use of nuclear transfer (par bridging pages 5 and 6 of Office Action, mailed10/19/2006) and that the activation and deactivation of genes during differentiation is a complex process probably determined by many factors, that simple activation or deactivation processes such as the use of chromatin altering agents will most likely not resolve the complexity of reprogramming somatic nuclei (p. 6 of same Office Action). The enablement rejection of record also provides the art of Keohane et al, which stated that deacetylation may be more important for stabilization and maintenance of the inactive state than initiation, which would be contrary to the instantly claimed methods, and Eickoff et al, which teaches that tichostatin A, as claimed, alters gene expression in a cell and induces it to undergo apoptosis, not dedifferentiation. You et al also provides contradictory teaching to the instantly claim

method by demonstrating the trichostatin A treatment as claimed reduces telomerase expression and activity in human cells.

Applicant acknowledges these complexities in the art but suggests that the instant specification provides reduction to practice of the instant method which results in reprogramming keratinocytes to become non-keratinocytes (p 3 of remarks, filed 1/22/2007).

These arguments of reduction to practice are not considered persuasive because, as previously discussed above, the reduction to practice discussed above does not adequately demonstrate the keratinocytes were reprogrammed to become functional cells of another lineage. The working examples only demonstrate that treating with chromatin altering agents will result in expression of non-keratinocytes genes. The specification does not provide any evidence such as functional assays or any other type of data to demonstrate that the instant gene expression profiles are not just an aberration associated with the treatment of chromatin altering agents and distinguish the treated cell as functional cell representative of another cell type other than a keratinocyte.

Therefore, given that Applicant's arguments have not been found persuasive and Applicant did not amend the claims, the enablement rejection of record is maintained for reasons discussed above and previously made of record.

4. No claimed are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcia S. Noble

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